REMARKS

Claims 7 to 10, 15, and 17 are pending in this application. Applicants have cancelled claims 1 to 6, 11 to 14, and 16 as directed to a non-elected invention. Claims 7, 8, and 17 have been amended. Support for these amendments can be found throughout the specification, particularly at page 1, lines 22 to 24; page 15, lines 15 to 17; and page 16, lines 3 to 7. Amendments to the specification were made to correct typographical errors. The reference to a prior U.S. Patent No. had two numbers transposed. The correct patent number appears in the specification at page 15, line 16, and page 16, line 5. Thus, these amendments add no new matter to the present application.

The Invention

The invention is based on the discovery that oligosaccharides derived from chlamydial glycolipids can be used to raise an immune response in a vertebrate that is protective against chlamydial infections. The oligosaccharides can be cleaved directly from chlamydial glycolipids and/or chemically synthesized, and linked to a carrier group to form a composition that can be used as a chlamydia vaccine.

Restriction

Applicants confirm the election of Group II, made on November 8, 2001, and have cancelled non-elected claims 1 to 6, 11 to 14, and 16 without prejudice.

Claim Objections

The Office Action objected to claim 7 for recitation of the term "GLXA." For the sake of clarity, applicants note that claim 7 does not recite the term "GLXA." However, the term is recited in claim 8, which applicants have amended. As amended, claim 8 recites "a chlamydial glycolipid exoantigen," thus obviating any objection to this claim based on recitation of the term "GLXA." Applicants therefore request that the objection be withdrawn.

35 U.S.C. § 102

Claims 7 and 9 have been rejected as allegedly anticipated by Svenson et al. (*J. Immun. Methods* 25(40):323-335 (1979)). The Office Action states (at page 3, lines 1 to 3):

> Svenson et al teach a composition comprising Salmonella specific oligosaccharides coupled to carriers using 2-(4-aminophenyl)ethylamine as the linker (see the Abstract).

Svenson discloses methods for coupling oligosaccharides isolated from the *Salmonella typhimurium* O-polysaccharide chain (O antigen), which is a component of *S. typhimurium* lipopolysaccharide (LPS), to macromolecular carriers.

Although the Office Action points to no particular evidence in Svenson that this publication discloses the compositions recited in claims 7 and 9, the Office Action asserts that the burden is on applicants to show that the presently claimed compositions are different from those in Svenson.

Applicants respectfully submit that Svenson does not anticipate claims 7 and 9 because the oligosaccharides used in Svenson are not obtained from chlamydial glycolipids, and differ chemically from oligosaccharides taught by the present invention. The oligosaccharides used in Svenson's method are portions of the O-antigen of *S. typhimurium*, strain SH4809. In gram-negative bacteria, O antigens differ among species to such a large extent that they are used in the field of microbiology to define species and subspecies of bacteria (see, e.g., Neidhardt et al., Physiology of the Bacterial Cell a Molecular Approach). The genus *Salmonella* itself contains over 1000 distinct types having different antigenic specificities in their O antigen (Brock et al., Biology of Microorganisms, 7th ed.). The O-polysaccharide of *S. typhimurium* SH4809 is therefore likely to be specific to bacteria of the genus *Salmonella*, and possibly specific to strain SH4809. The oligosaccharides obtained from the O-polysaccharides can also be expected to be specific to bacteria of the genus *Salmonella*, which is made clear by the fact that Svenson itself characterizes the oligosaccharides as "*Salmonella* specific oligosaccharides" (see, e.g., the title of Svenson). Furthermore, Svenson provides a schematic representation of the O-antigen specific oligosaccharide in Fig. 1, which clearly shows that this oligosaccharide lacks gulose sugar units.

The presently claimed oligosaccharides, on the other hand, are derived from chlamydial glycolipids, e.g., GLXA. The polysaccharides associated with GLXA include the unique sugar residue gulose (and/or derivatives thereof), as well as mannose and possibly galactose, which appear to be arranged in repeating units of guluoronic and mannuronic acids (see U.S. Patent No. 5,840,297 at column 28, lines 61 to 64, and column 5, lines 41 to 46; attached hereto at Tab 1; hereinafter "the '297 patent"). The '297 patent suggests (at column 29 lines 10 to 12), based on composition analysis, that the immunogenic epitope of GLXA is gulose together with mannose and galactose. Applicants respectfully submit that *S. typhimurium* O-polysaccharides (and oligosaccharides isolated therefrom) do not possess such chemical characteristics, e.g., they do not include the relatively rare sugar residue gulose (see Svenson at Fig. 1).

Thus, applicants submit that the oligosaccharides used in the method of Svenson are not obtained from chlamydial glycolipids, and differ chemically from the oligosaccharides taught by the present invention. Because Svenson does not disclose all of the elements recited in claims 7 and 9, Svenson does not anticipate these claims. Applicants therefore request that the present rejection be withdrawn.

Claims 7 and 9 were also rejected as allegedly anticipated by Kamath et al. (*Glycoconjugate Journal*, 13:315-319 (1996)). As with Svenson, the Office Action points to no evidence in Kamath that this publication discloses the compositions recited in claims 7 and 9. However, the Office Action asserts that the burden is on applicants to show that the presently claimed compositions are different from those in Kamath.

Applicants respectfully submit that Kamath does not anticipate claims 7 and 9 because Kamath, like Svenson, fails to disclose an oligosaccharide obtained from, or chemically similar to, an oligosaccharide obtained from a chlamydial glycolipid.

Kamath describes a method for coupling amino-derivatized sugars to amino groups on proteins. In particular, Kamath describes a method for coupling 8-methoxycarbonyloctyl glycosides to bovine serum albumin. The mono- and oligosaccharides used in Kamath's method are illustrated in Kamath at "Scheme 1," page 317, and include the residues N-acetylglucosamine, galactose, glucose, and fucose. As discussed above, the polysaccharides associated with chlamydial glycolipids such as GLXA include gulose (and/or derivatives

thereof), mannose and possibly galactose, which appear to be arranged in repeating units of guluoronic and mannuronic acids. None of the oligosaccharides described in Kamath have such characteristics, or contain any gulose sugar residues. Thus, none of the oligosaccharides used in Kamath could be characterized as an oligosaccharide similar to, or obtained from, a chlamydial glycolipid, because they differ chemically from the presently claimed oligosaccharides.

Because Kamath, like Svenson, does not disclose all of the elements of claims 7 and 9, Kamath does not anticipate these claims. Thus, applicants request that the present rejection be withdrawn.

Claim 15 was rejected as allegedly anticipated by Stuart et al. (*Immunology*, 68:469-473 (1989)). Stuart describes the results of a study that investigated the relevance of GLXA to natural chlamydial infections, immunopurification of GLXA from supernatants of infected cultures, and biochemical characteristics of GLXA.

Applicants respectfully traverse this rejection because Stuart does not disclose purified GLXA that is free of other components. Rather, the preparations described in Stuart include GLXA and a mixture of other materials. These contaminating materials were visualized in Stuart using sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) and silver staining (see, e.g., Stuart at Figs. 2 and 5). Stuart itself acknowledges that the preparations contain contaminants, stating (at page 472, lines 28 to 35):

> The SDS-PAGE analyses also indicate that a variety of molecular weight species exist and are detectable, with bands also occurring at 43,000 MW and 30,000 MW. This overall pattern is consistent with different serovars and appears to be identical whether the GLXA is isolated by monoclonal antibody affinity chromatography or dissociation of polyclonal antibody-antigen complexes isolated by molecular shift chromatography.

Based on the statement quoted above and the data published in Stuart, it is clear that Stuart does not disclose purified GLXA that is free of other components. The GLXA taught by the present application and recited in claim 15, on the other hand, is highly purified and free of other components. Because Stuart does not disclose all of the elements of claim 15, Stuart does not anticipate the present claim. Thus, applicants respectfully request that the present rejection be reconsidered and withdrawn.

35 U.S.C. § 103

Claims 7 to 10, 15, and 17 were rejected as allegedly obvious over McDonald et al. (U.S. Patent No. 5,716,793) in view of Semprevivo (*Carbohydrate Research*, 177:222-227). Applicants respectfully traverse this rejection for the reasons discussed below.

In support of the finding of obviousness, the Office Action states (at page 5, line 20, to page 6, line 3):

> It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to use the 2-(4-aminophenyl)ethylamine linkers as taught by Semprevivo to conjugate the chlamydial glycolipid exoantigen (GLXA) to the labeled antibodies in the composition of MacDonald et al because Semprevivo demonstrates extremely consistent results that show that neoantigens produced by coupling derivatized oligosaccharides to protein react strongly with a preformed specific anti-oligosaccharide antibody (page 227).

Applicants respectfully disagree for the following reasons. McDonald et al. describes methods for detecting chlamydia in biological samples. Specifically, the methods described in McDonald involve contacting biological samples with GLXA-Ab_1 or – Ab_3 to detect the glycolipid GLXA in a biological sample. McDonald does not disclose smaller oligosacharides obtained from (or corresponding to) this chlamydial glycolipid. McDonald does not even suggest that useful individual oligosaccharides should be (or could be) cleaved or chemically synthesized from GLXA. McDonald does not disclose or suggest that such an oligosaccharide could be coupled to a carrier, nor does it suggest methods for performing such coupling.

The Office Action also cites Semprevivo. However, this publication does not provide the information missing in the primary reference. Semprevivo describes a method for derivatizing oligosaccharides from the eukaryotic organism *Leishmania mexicana amazonensis*. Semprevivo indicates that similar methods have been utilized for other eukaryotic organisms, such as *Leishmania tropica*, *Leishmania donovani*, *Trichomonas vaginalis*, *Schistosoma mansoni*, and *Nematospiroides dubius*. Semprevivo does not disclose any chlamydial glycolipids, such as GXLA. Further, Semprevivo does not disclose, or even suggest, that Semprevivo's methods could have been utilized with glycolipids from prokaryotes of the genus *Chlamydia*, or for that matter, any other prokaryotic organism.

Applicants submit that a person skilled in the art would not have been motivated by Semprevivo to modify the methods described in McDonald to create the compositions recited in claims 7 to 10, 15, and 17. Neither publication suggests that useful oligosaccharides could, or should have been isolated from chlamydial glycolipids, or that they could be coupled to carriers using a method such as that described in Semprevivo. In fact, Semprevivo itself provides the suggestion that the coupling methods described in Semprevivo would not have worked with bacterial glycolipids, and thus teaches away from such an endeavor. Applicants point out that Semprevivo's method relies on trifluoroacetolysis (see, e.g., Semprevivo at page 223, lines 19 to 20) for the release of reducing oligosaccharide residues. Trifluoroacetolysis specifically cleaves glycosidic bonds between carbohydrates and unsaturated bases of specific ceramides (see, e.g., Gunnarsson et al., *Acta Chem. Scand.*, B 38:603-609 (1984); attached hereto at Tab 2). Applicants further point out that any person skilled in the art would have recognized that while most eukaryotic glycolipids are ceramide-based glycolipids, most prokaryotic glycolipids are glycerol-based lipids. Because trifluoroacetolysis cleaves glycosidic bonds between carbohydrates and unsaturated bases of specific ceramides, and because most prokaryotic glycolipids lack ceramide, a skilled practitioner would have expected that Semprevivo's methods could not have been used with chlamydial or any other prokaryotic glycolipid. Thus, applicants submit that a person skilled in the art would not have been motivated by Semprevivo to modify the methods described in McDonald to create the compositions recited in claims 7 to 10, 15, and 17.

It appears that the Office Action relies on the present application to provide a roadmap to show how to combine the cited references. However, to support a proper prima facie case of obviousness, the prior art, not applicants' application, must contain the requisite motivation to combine all the cited references. Any other analysis of the art is hindsight, which the courts have long prohibited. For example, in its analysis of whether or not the idea of using a particular cloning method was obvious, the Federal Circuit in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991) found that:

> [T]he realization of that idea [to use a particular cloning strategy] would not have been obvious. There were many pitfalls. *Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious* (emphasis added).

The prior art must suggest the combination of the prior art teachings and that such a combination would have a reasonable likelihood of success. That it may be "obvious to try" such a combination is not the proper standard in an obviousness analysis. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) (an invitation to try an experiment is not the proper test for obviousness); In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529 (Fed. Cir. 1988):

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. ...(Citations omitted) Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

Applicants submit that neither of the publications cited in the Office Action, singly or in combination, suggest developing the compositions of the present invention. Thus, applicants respectfully request that the present rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Attached is a marked-up version of the changes being made by the current amendment. The mark-up version is entitled "Version with Markings to Show Changes Made." Enclosed is a check for $200 for the Petition for Extension of Time fee for a two month extension. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket Number 08952-008001.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Specification:

The paragraph at page 1, lines 22 to 27 has been amended as follows:

The invention is based on the discovery of an effective chlamydial vaccine based on oligosaccharides derived from one or more chlamydial glycolipids, such as the chlamydial glycolipid exoantigen (GLXA; see, e.g., U.S. Patent No. 5,840,297 [5,840,279]). These oligosaccharides, which are cleaved from naturally occurring glycolipids or chemically synthesized, are then covalently linked to a carrier group to form a composition that can be used as a chlamydia vaccine.

The paragraph at page 6, lines 13 to 29 has been amended as follows:

Glycolipids from *Chlamydia* can be isolated by any method known in the art, or by the methods described below. For example, cells (e.g., McCoy cells [a mouse fibroblast cell line], the mouse macrophage cell line J774A.1, or HeLa 229 cells) can be infected with *Chlamydia trachomatis* (B serovar) *in vitro* at an MOI of 10. At 24 hours post-infection 100 U/ml of penicillin are added to increase production of GLXA into the supernatant. GLXA is a chlamydial exoantigen that is secreted into the medium in infected cell cultures and has a molecular weight of about 58 to 62 kDa. At 96 hours post-infection, the GLXA is isolated from the supernatant using standard methods or the methods described in the Example below. Standard methods include hydrophobic gel filtration; treatment with DNAse, RNAse, and proteinase K; solvent extraction; and affinity chromatography (using, e.g., the antibodies described in U.S. Patent No. 5,840,297 [5,840,279]). Additional details regarding chlamydial glycolipid isolation can be found in Stuart et al., "Genus glycolipid exoantigen from Chlamydial trachomatis: component preparation, isolation, and analysis," In: Chlamydial Infection, Oriel et al., eds., 1986, Cambridge University Press, England; Troidle, "Characterization of a genus specific chlamydial antigen," Ph.D. thesis, 1992, University of Massachusetts, Amherst, MA.; and Stuart et al., Current Microbiology 28:85-90, 1994.

In the Claims:

Claims 1 to 6, 11 to 14, and 16 have been cancelled without prejudice as directed to a non-elected invention.

Claim 8 has been amended as follows:

--8. (Amended) The composition of claim 7, wherein the glycolipid is a chlamydial glycolipid exoantigen [GLXA].--